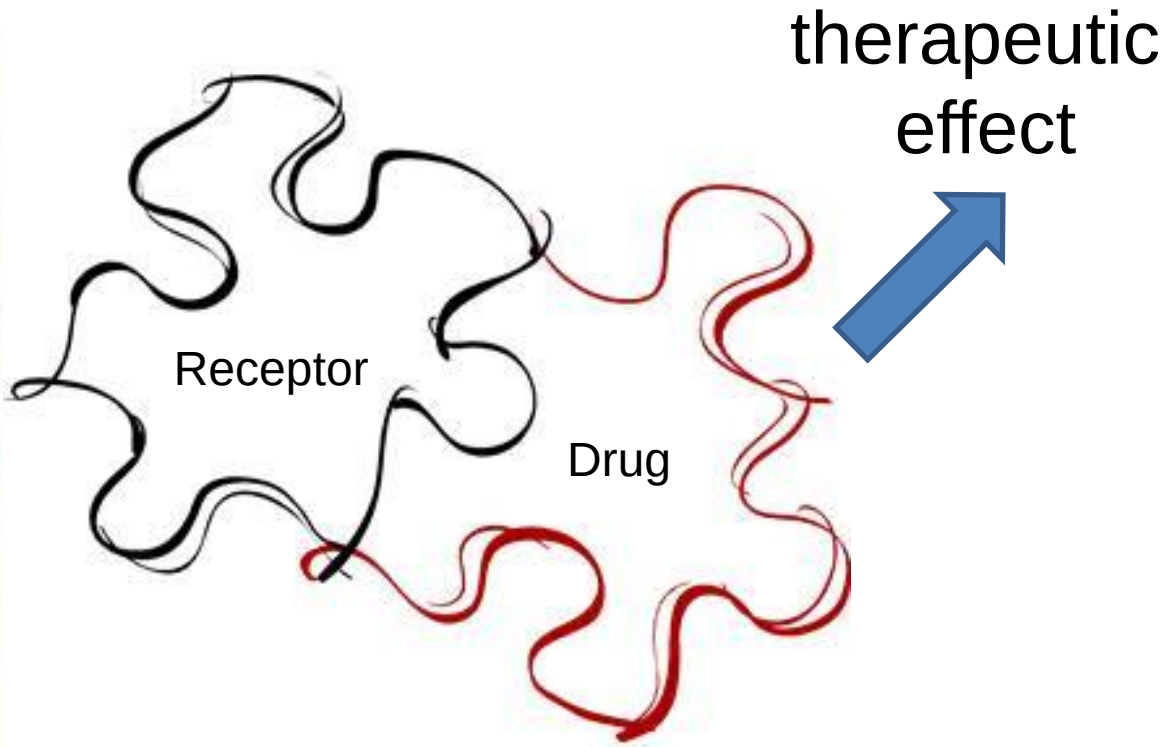
THE UNIVERSITY of York

Drugs Down the Drain: How can we assess and manage the impacts of medicines in the natural environment?

Alistair B A Boxall
Environment Department


OcuFresh
Sleep Well
Aquaphor
RAHUA
M LAB.
PerioWash
Complete Oral Care

Drug receptors



Many receptors also occur in organisms in the natural environment

Effects on behaviour

Rebecca Klaper, Great Lakes Water Institute

Fathead minnow -

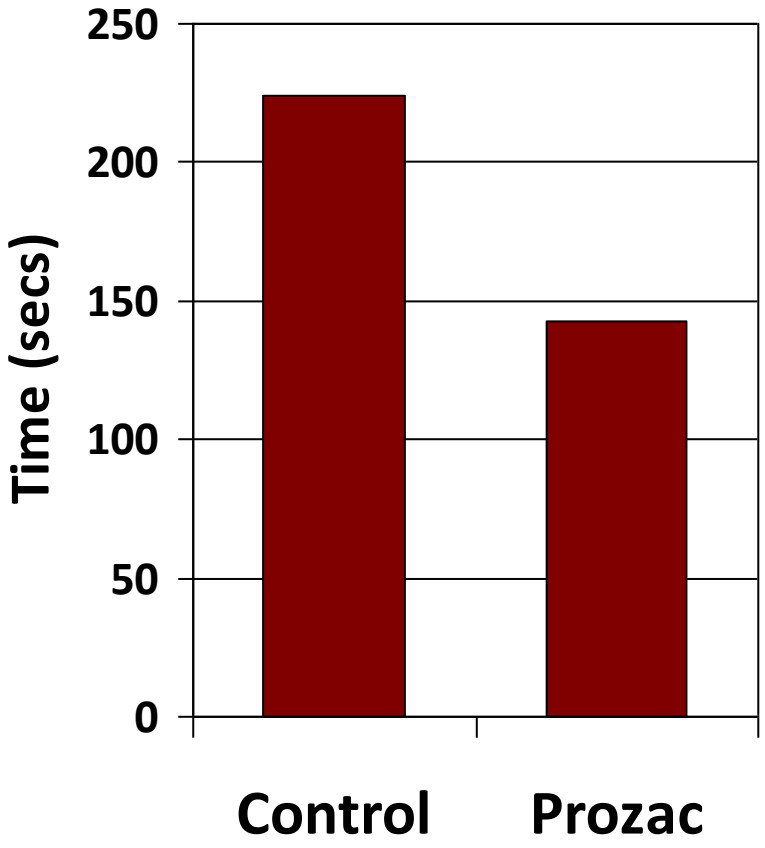
Lifecycle exposure

to Fluoxetine

100 ng/L

Behavioural change – males sitting under tiles, not pursuing females. Time spent on breeding behaviours was very low.

Effects of Prozac on woodlice



‘Nine species of vultures in the wild numbered 40 million birds in the early 1980s. Today, only about 60,000 birds are left’

(Vibhu Prakash, Bombay Natural History Society)

Presentation today

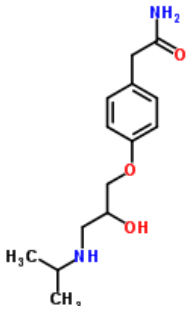
- Focus on systems in the UK
- What is the level of exposure at the landscape level?
- Could there be impacts?
- Could we manage these impacts?

Monitoring in the UK

- Monthly monitoring of 16 compounds across 4 catchments

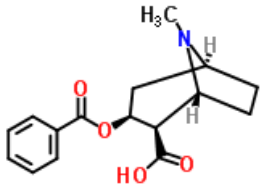
Location	Population	Number of treatment plants upstream of sampling point	Types of STPs†	Average water residence between discharge and sampling (d)
Midlands	402227	17	SAS 1, SB 5, TA 3, TB 8	**1.27**
Southern England	2071445	81	SAS 12, SB 22, TA 19, TB 28	**2.33**
Southern England	395581	27	SAS 2, SB 11, TA 8, TB 6	**2.42**
South East England	**177801**	**14**	**SAS 2, SB 3, TA 4,TB 5**	**1.46**

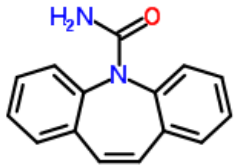
SAS - Secondary Activated Sludge; SB - secondary biological filter; TA - Activated Sludge with tertiary treatment; TB - Biological filter with tertiary treatment.



atenolol

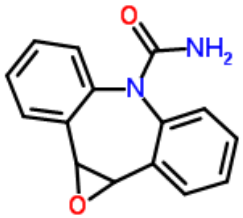
benzoylecgonine

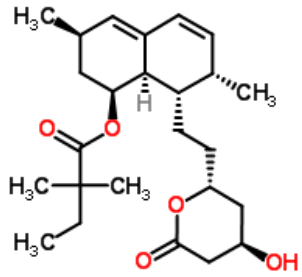




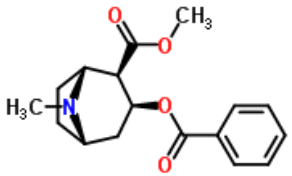
carbamazepine

carbamazepine epoxide

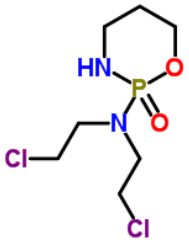




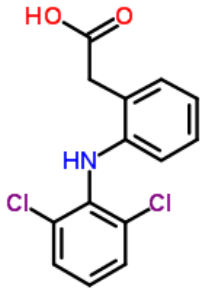
simvastatin



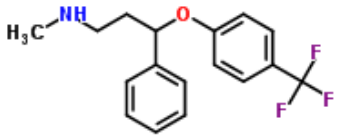
cocaine



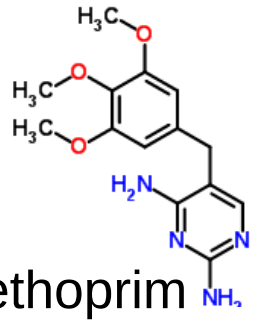
cyclophosphamide



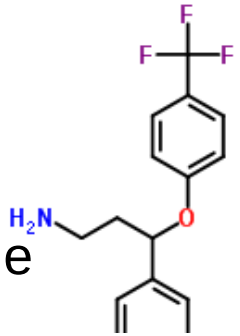
diclofenac



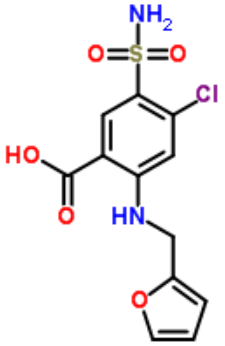
fluoxetine



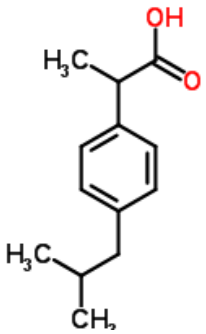
trimethoprim



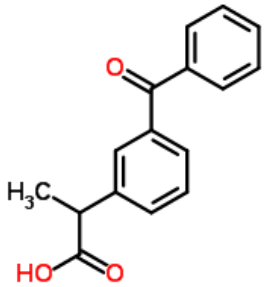
norfluoxetine



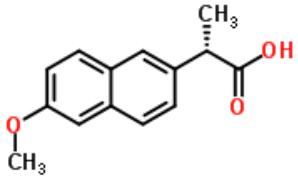
furosemide



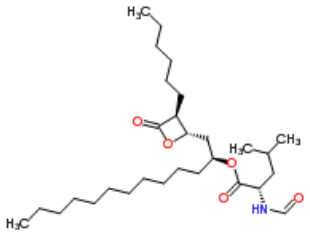
ibuprofen



ketoprofen

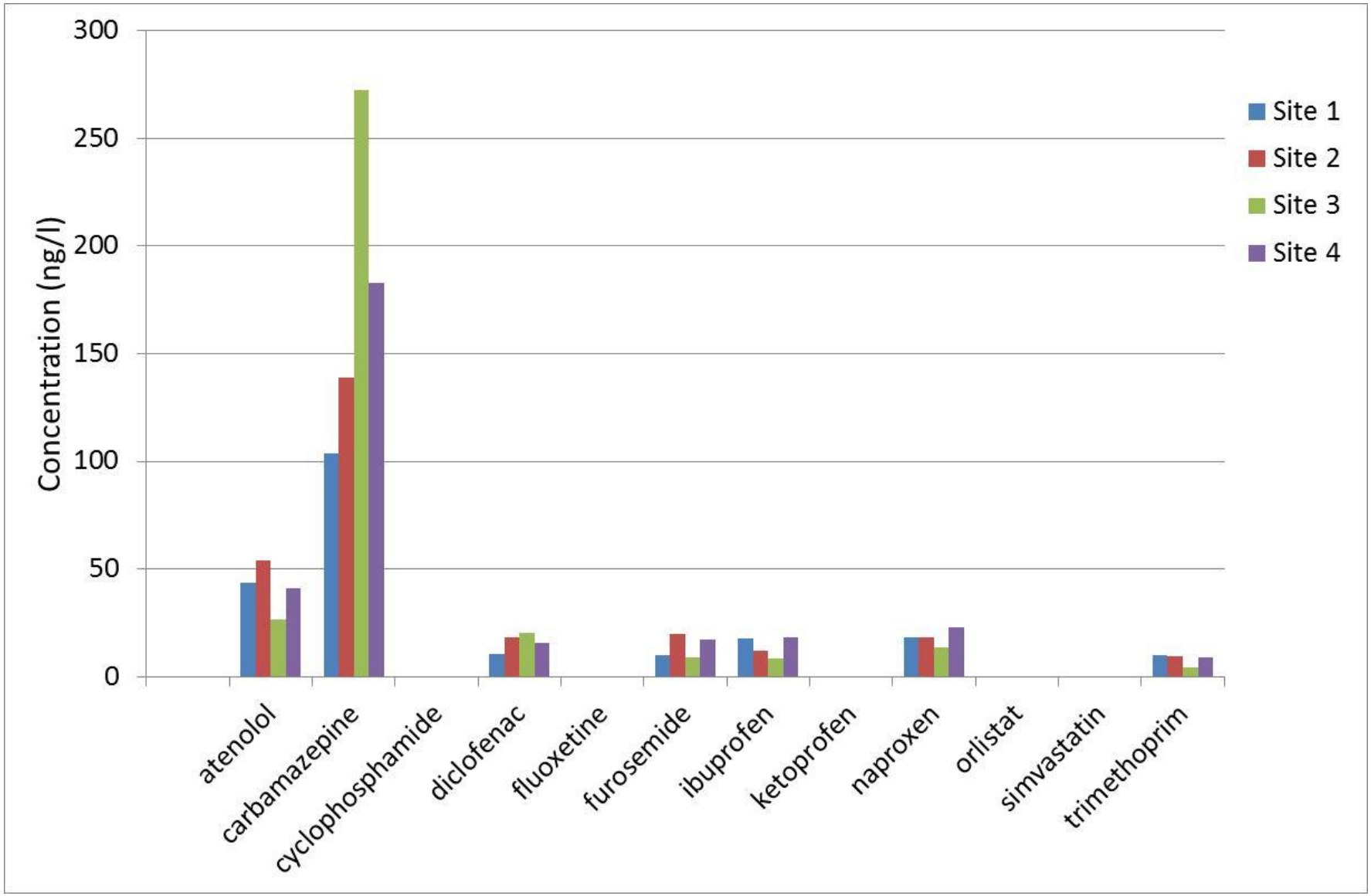


naproxen

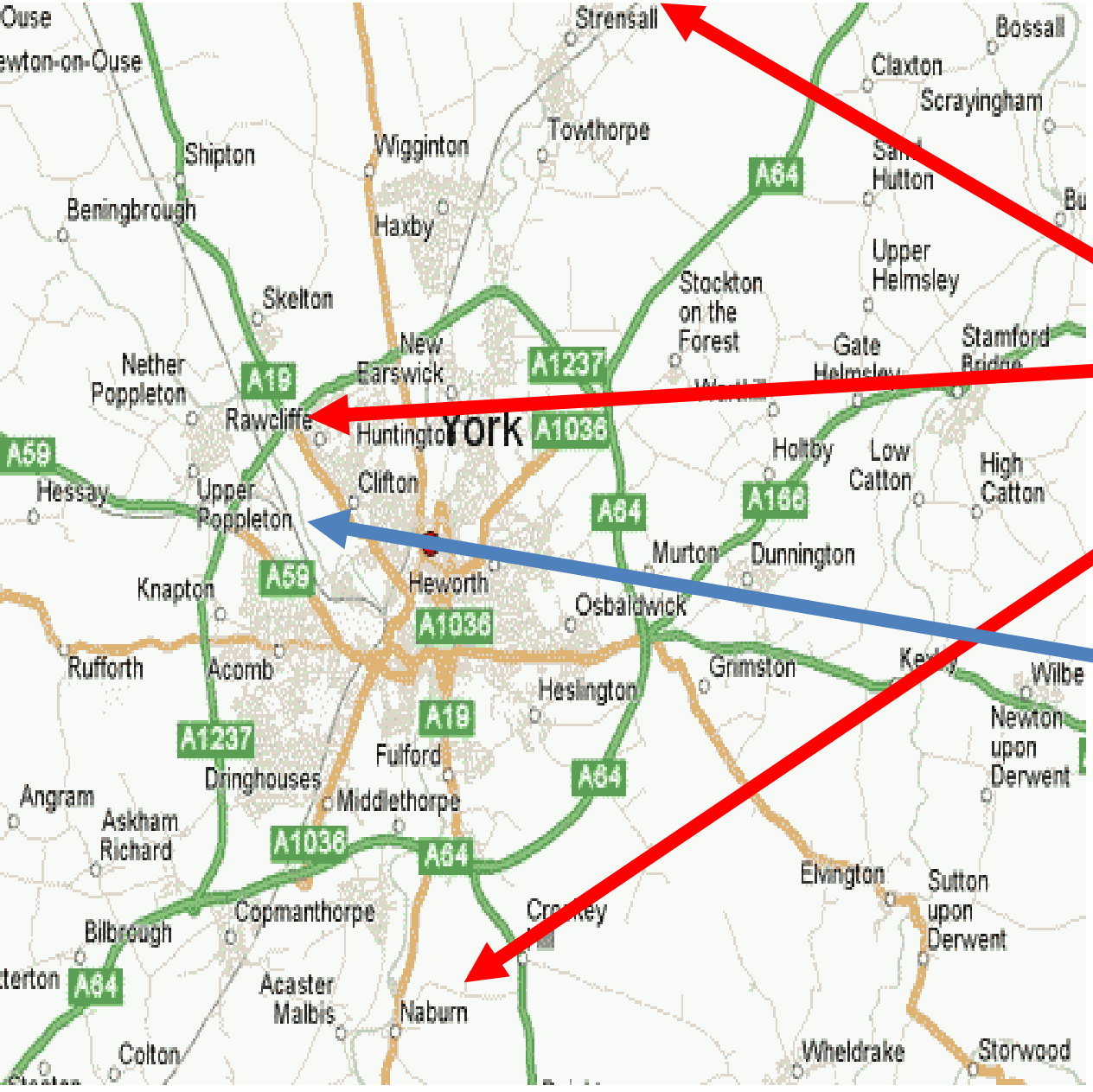


orlistat

Occurrence in UK rivers

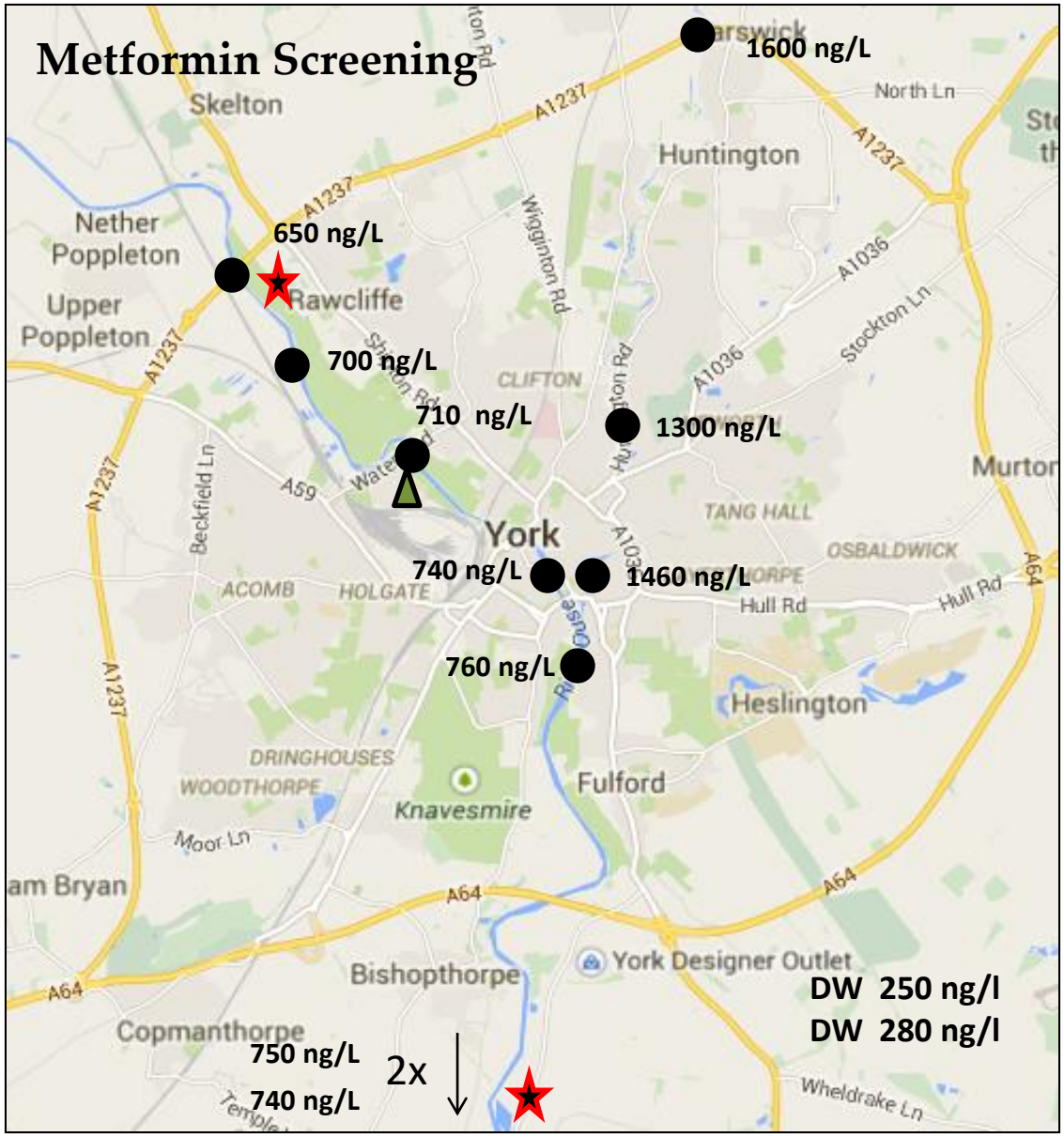


Situation in York



- STPs
  - Walbutts
  - Rawcliffe
  - Naburn
- Drinking water

Monitoring York



- Pilot study
- 10 sites
- 88 compounds
- Surface water and drinking water

Monitoring results

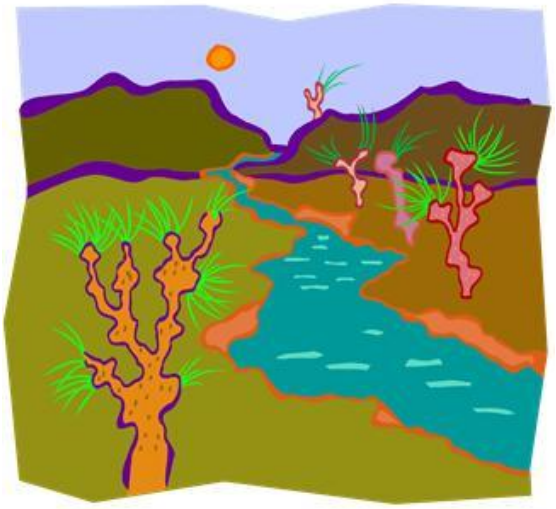
- River waters
  - 36 pharmaceuticals detected and quantifiable
  - 26 pharmaceuticals detected
  - 26 pharmaceuticals not detected
- Drinking water
  - 6 pharmaceuticals detected: metformin, nicotine, acetominophen, carbamazepine, cotinine, triamterene

Exposure modelling

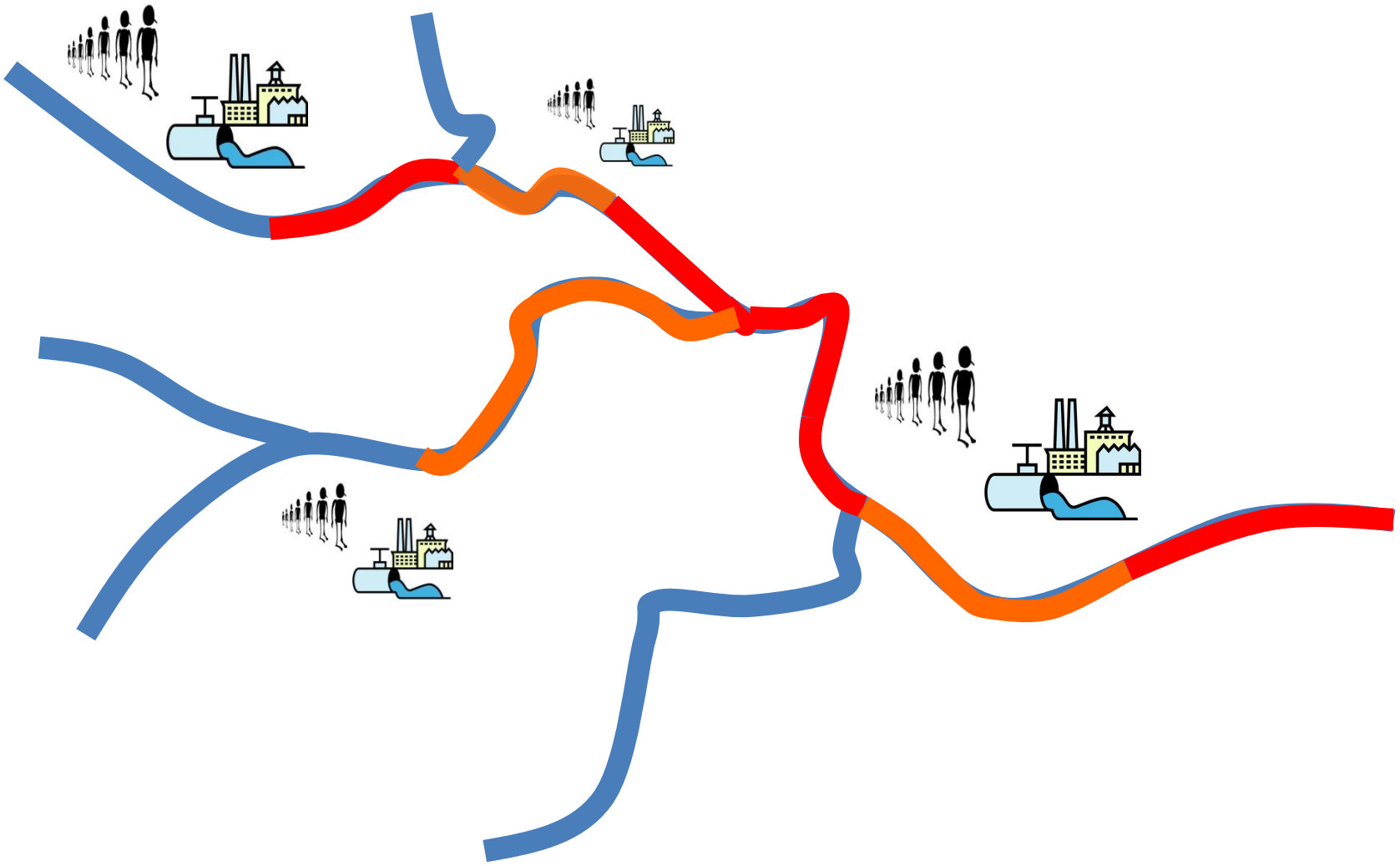
Usage: mg person^{-1} d^{-1}
Metabolism: fraction excreted
Population size: persons

Removal: fraction removed
Wastewater flow: m^3 d^{-1}

River flow: m^3 d^{-1}
In-river dissipation rates: d^{-1}

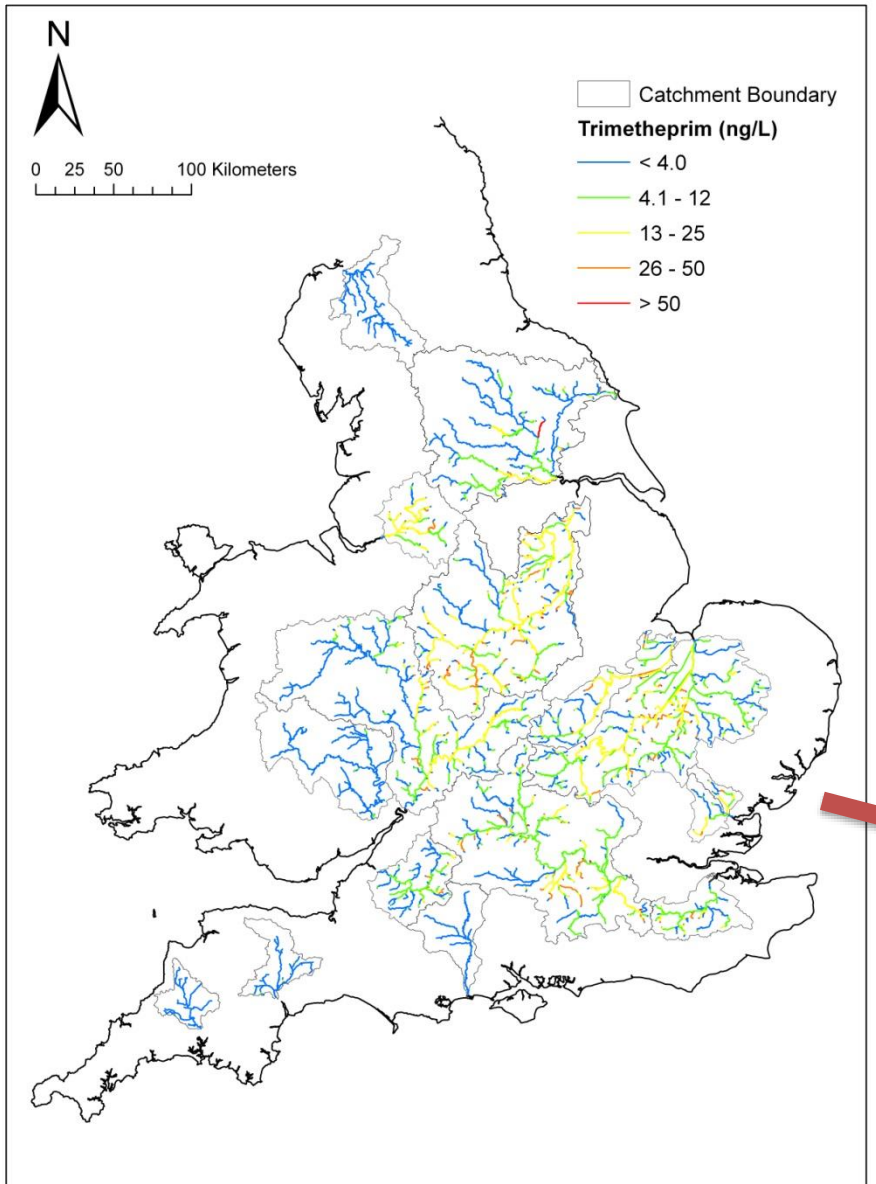


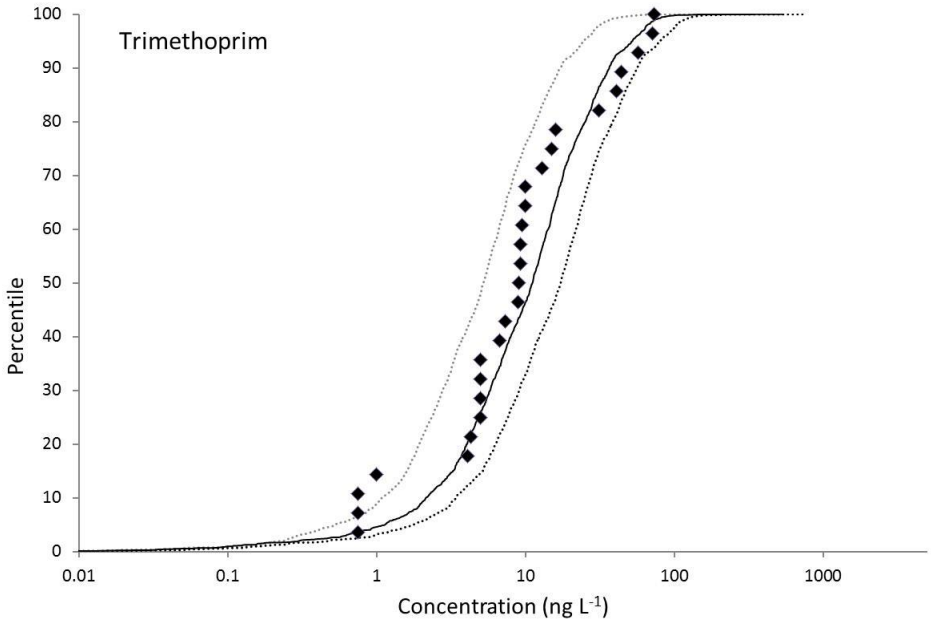
Low Flows 2000 WQX Model



Applied to monitored pharmaceuticals using both the forward and inverse modelling approaches

Concentrations of trimethoprim in monitored catchments



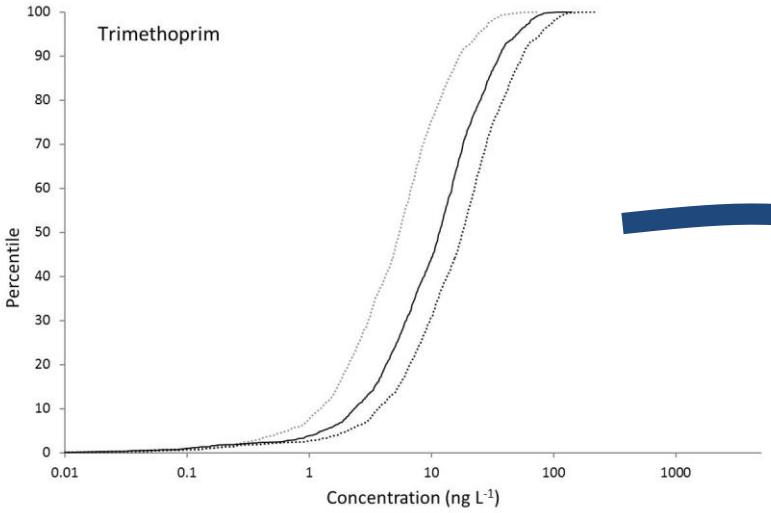


Predictions for each river reach obtained using mean, minimum and maximum removal rates obtained from the inverse modelling

Assessment of risks across the UK landscape

- 22 large catchments across England and Wales
- Serving a population of 21 M people
- Predictions obtained for 3117 river reaches
- Predictions compared to predicted no effect concentrations (and proposed quality standards) derived from available ecotoxicity data

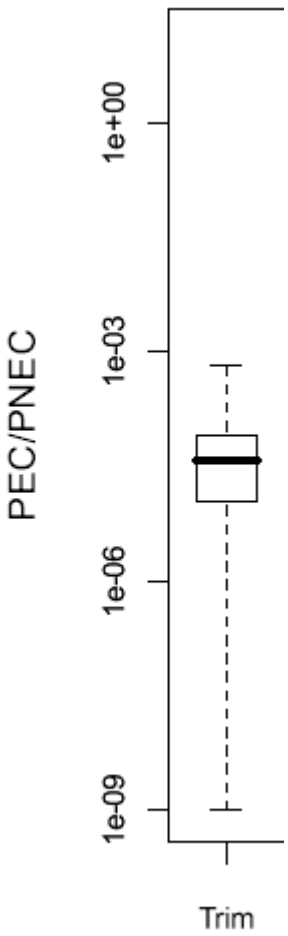
Risk characterisation



$$RCR = \frac{PEC}{PNEC}$$

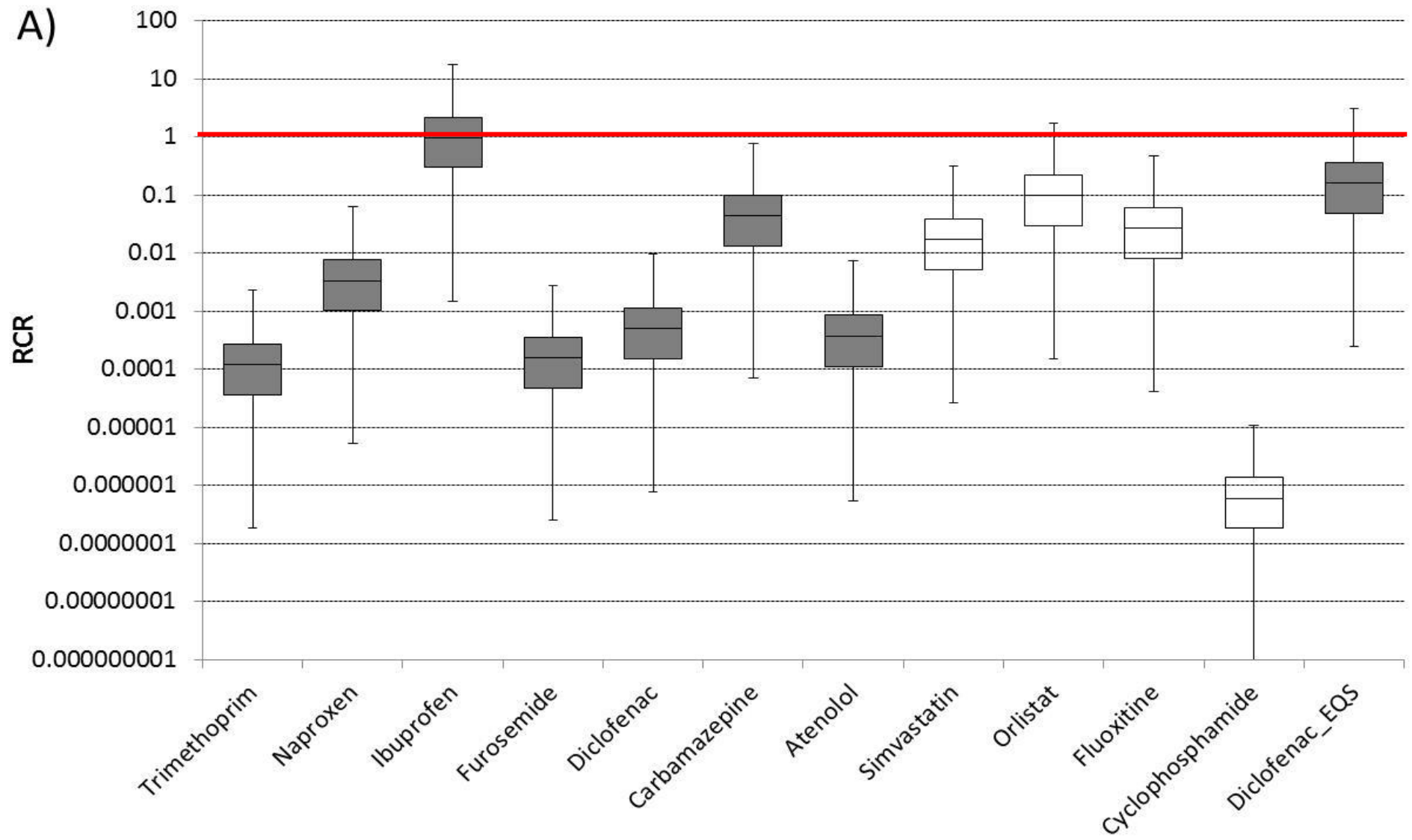
$$PNEC = \frac{ECx}{AF}$$

Or



WFD proposed EQS

Risk to UK Waters



THE INDEPENDENT

September 29, 2008

Tests for drugs in tap water

By Steve Connor, Science editor

Drinking water supplies are to be tested for the presence of prescription drugs amid fears that rivers are being contaminated by the growing quantity of pharmaceuticals flushed unwittingly down the drain.

The Government has commissioned scientists to test river water at intake points where it is abstracted for human consumption, The Independent can reveal. They will also test drinking water after it has been through the water-treatment cycle.

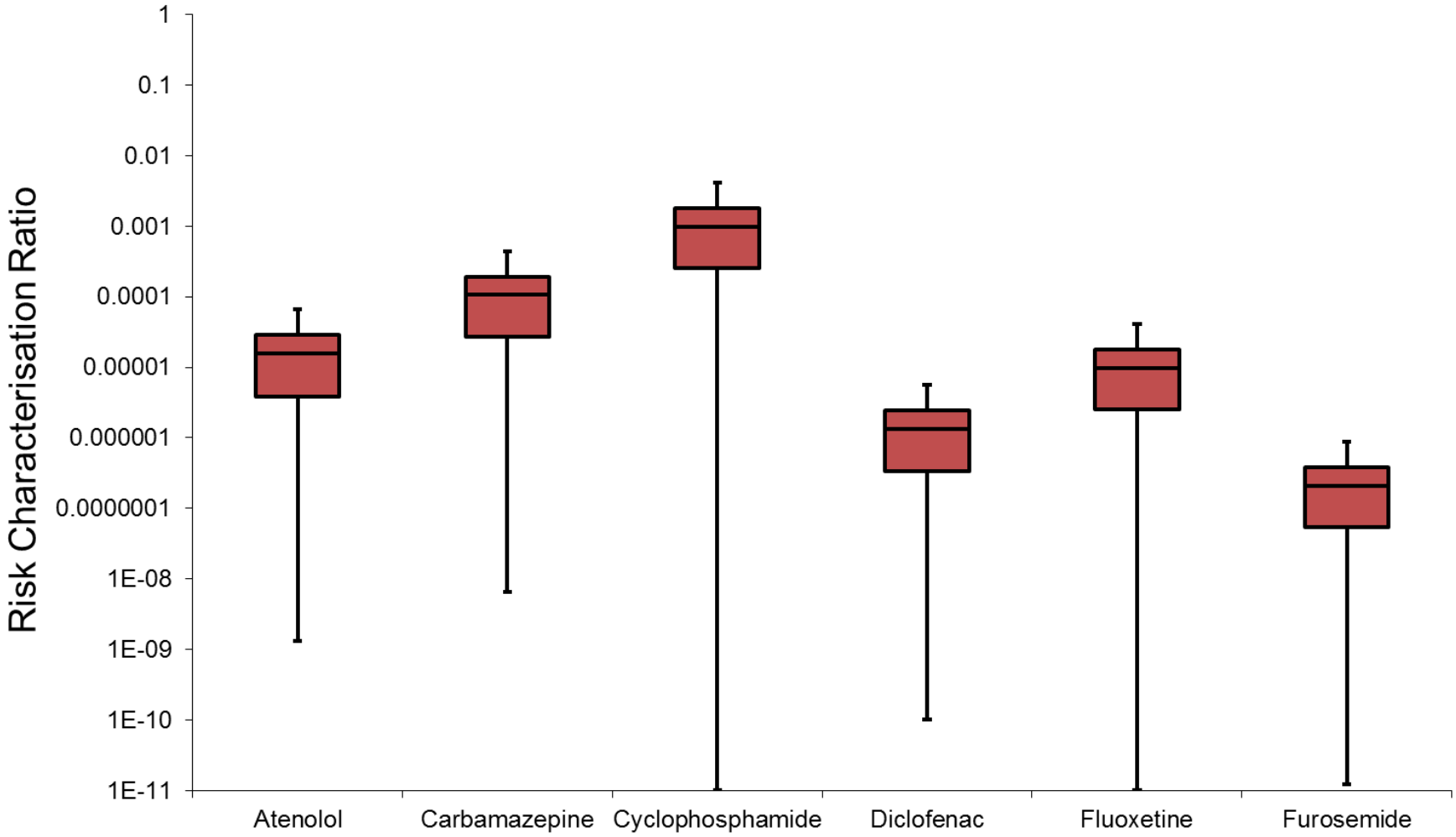
Under a pilot project to begin next year, supplies will be examined for about five of the most common and potentially dangerous prescription drugs. The experts will meet over the next few weeks to decide which drugs to look for and where testing should be carried out. However, an insider said this was likely to be at selected sites on the river Thames because its water-catchment area covered the most densely populated part of the country.

Powerful anti-cancer drugs are of particular concern as they can be excreted unaltered from the body into the sewerage system. They are thought to be potentially dangerous because they are highly toxic to dividing cells, are easily dissolved in water and are difficult to destroy by conventional water-treatment techniques.

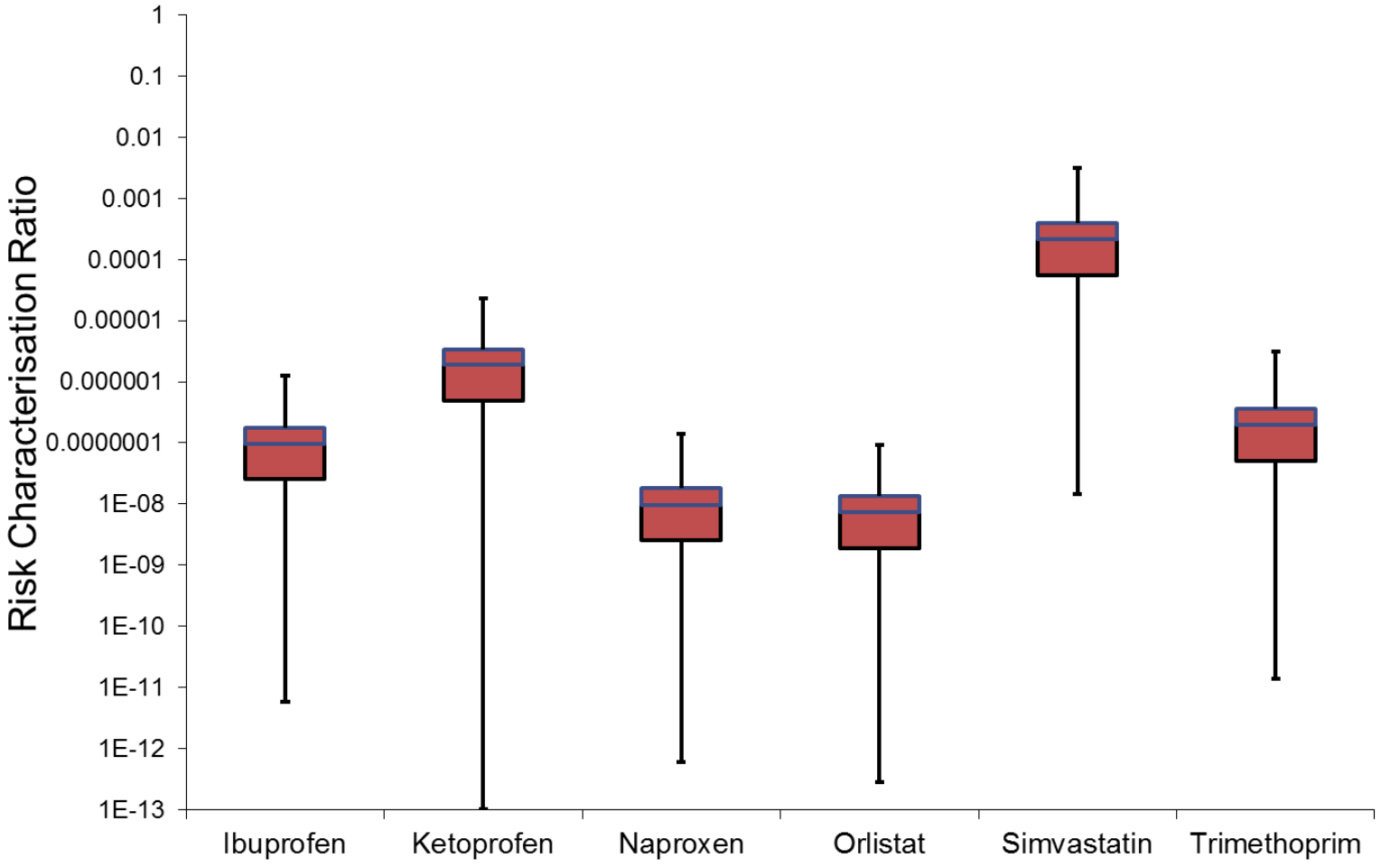
Risk to human health?

- 100 drinking water plants in the modelled river network
- Predictions of point of abstraction combined with DW treatment removal rates to estimate tap water levels
- Assumed individuals consumed 2 L of water per day and then compared estimated exposure to ADI

Human health risks



Human health risks

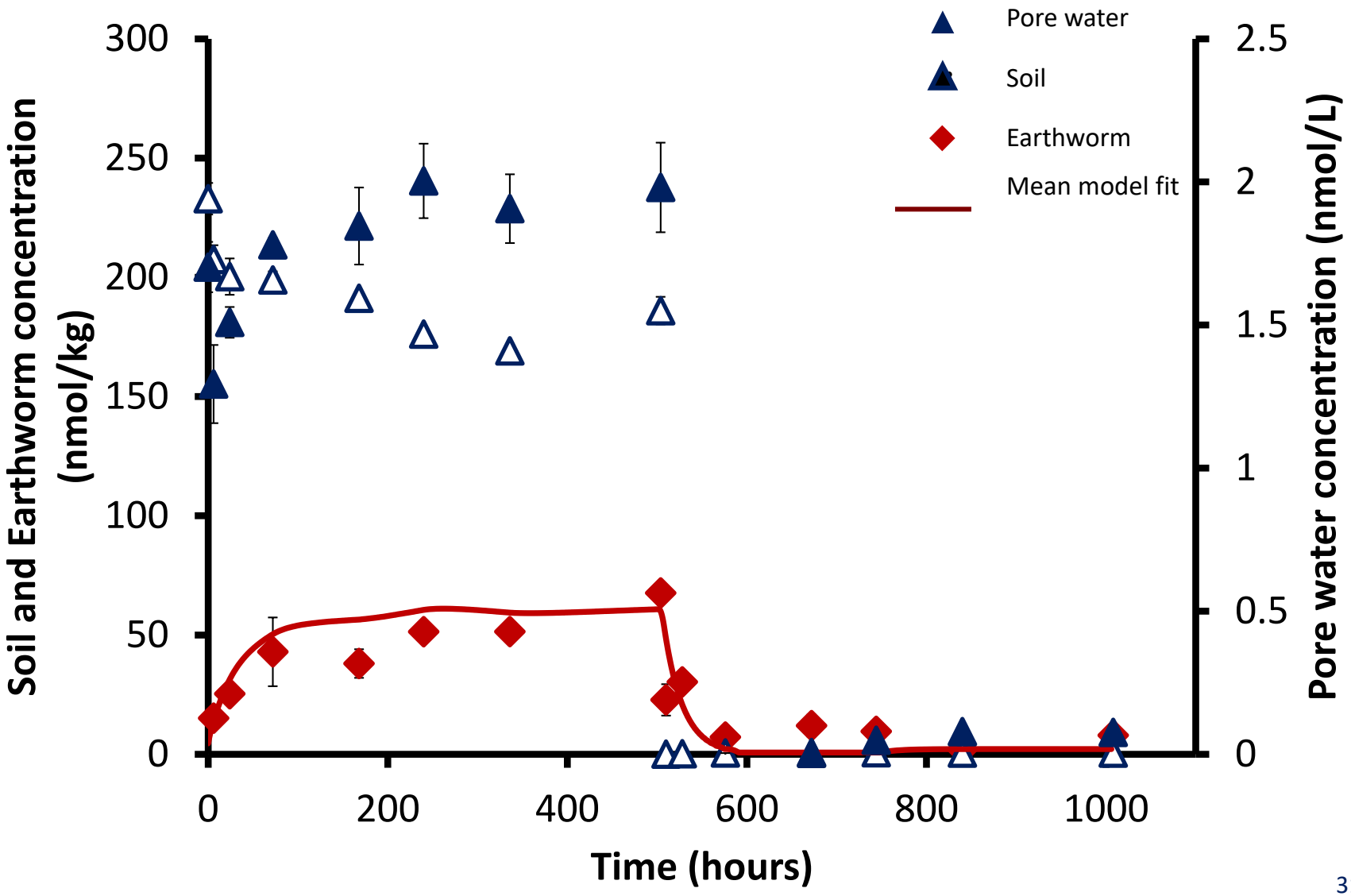


Effects on wildlife

Fluoxetine and food chains

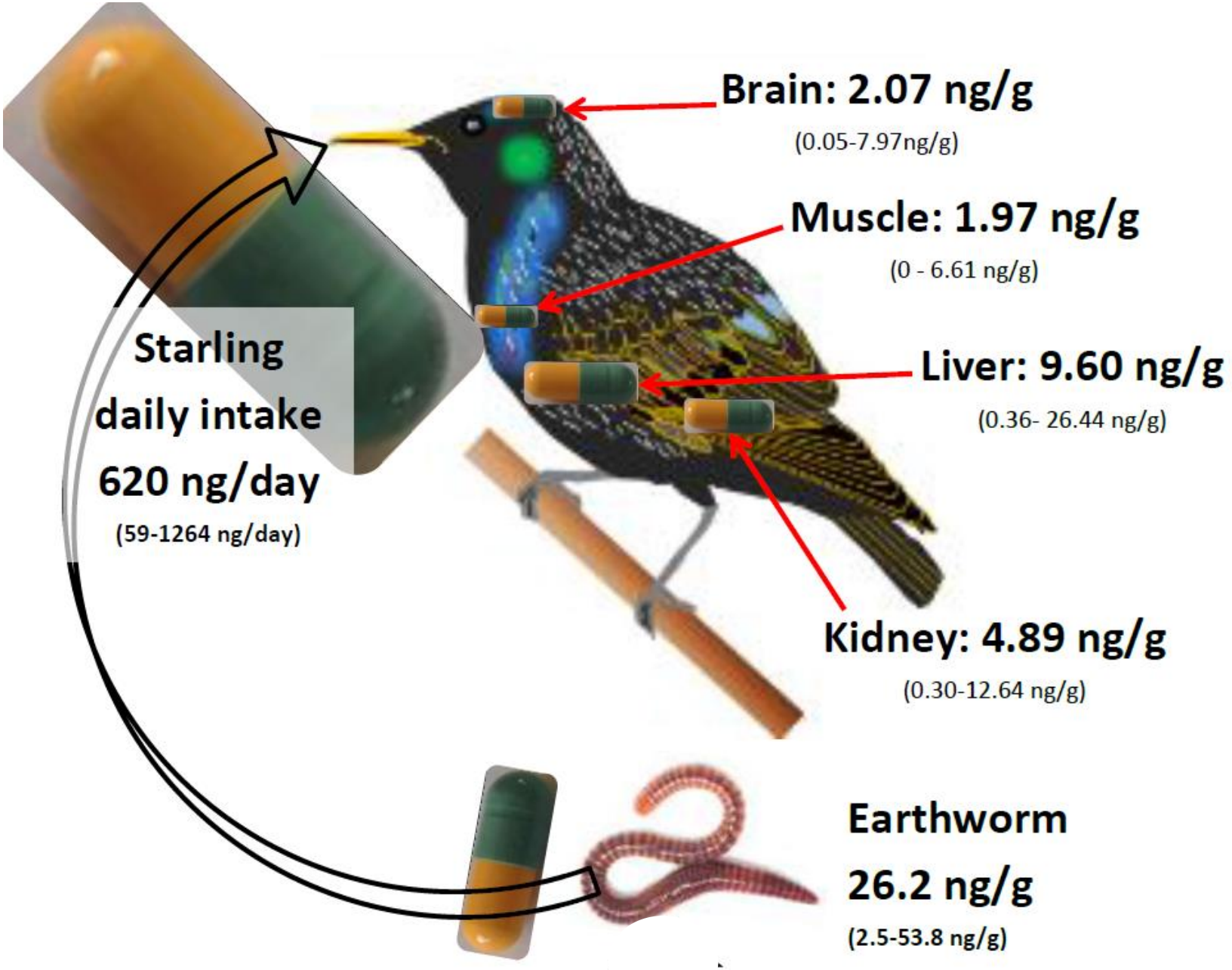
- Earthworm uptake
  - Soil properties
  - Species differences
- Starlings
  - 22 week aviary study at environmentally relevant exposures
  - ADME experiments
  - Behaviour and physiology studies

Uptake into worms



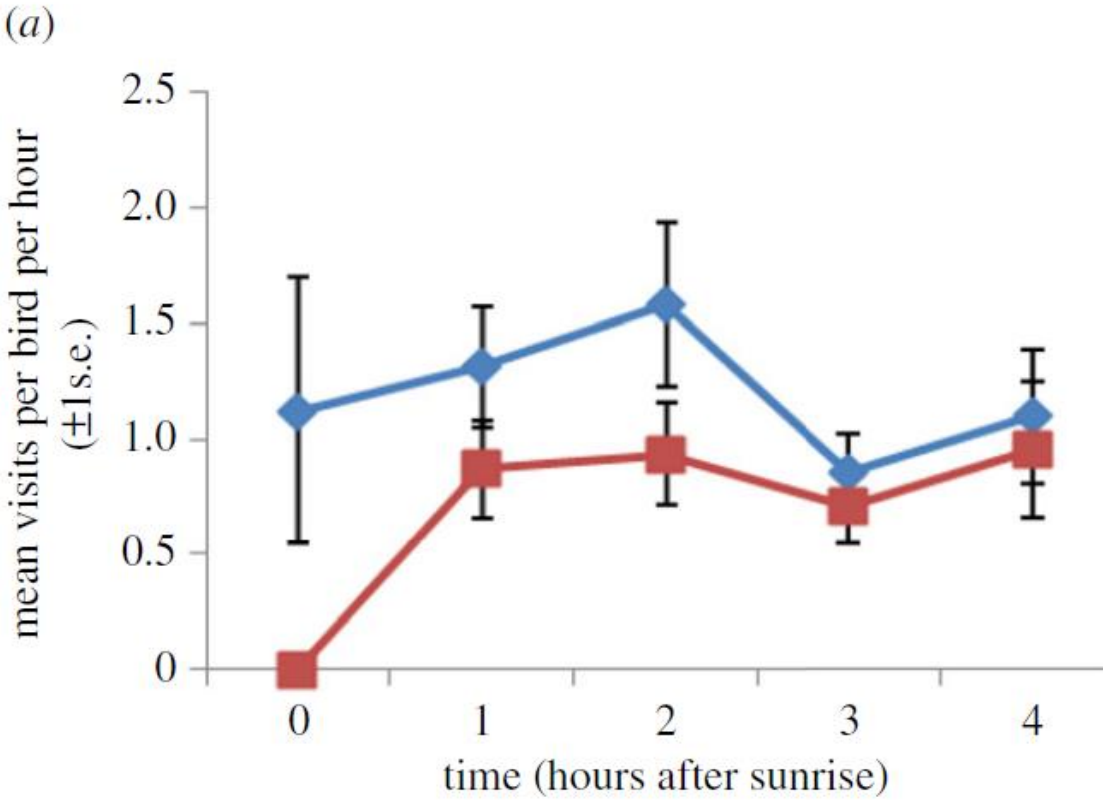
BCFs soil and species

Soil type	**Soil pH**	**Soil TOC**	***E. fetida***	***L. terrestris***
Clayey loam	6.3	1.89	30.8	66.9
Silty sand	5.1	0.74	20.42	-
Silty sand	6.6	0.97	19.74	-
Clayey loam	7.2	2.99	16.78	-
Clayey sand	7.2	1.23	19.18	-
Clayey loam	7.2	1.69	16.89	-


Brain: 2.07 ng/g
(0.05-7.97ng/g)
Muscle: 1.97 ng/g
(0 - 6.61 ng/g)
Liver: 9.60 ng/g
(0.36- 26.44 ng/g)
Kidney: 4.89 ng/g
(0.30-12.64 ng/g)
Starling
daily intake
620 ng/day
(59-1264 ng/day)
Earthworm
26.2 ng/g
(2.5-53.8 ng/g)

Impacts on starlings

- No effects
  - Boldness
  - Exploration
  - Activity
- Effects
  - Foraging behaviour
  - Physiology



Risk characterisation

- 45.5% of modelled river reaches (around 1500 reaches) have concentrations of ibuprofen of potential concern (fish hatching)
- 4.5% of modelled reaches (around 150 reaches) have concentrations of diclofenac of concern (histological effects)
- Risks to human health is low
- Potential effects on wildlife
- What can be done to control the risks?

Benign by design

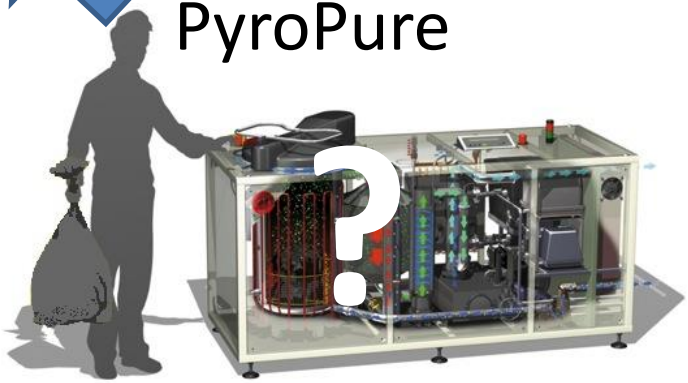
Upgrade sewage treatment plants

Reduced Pharmaceuticals in the environment

Stewardship schemes

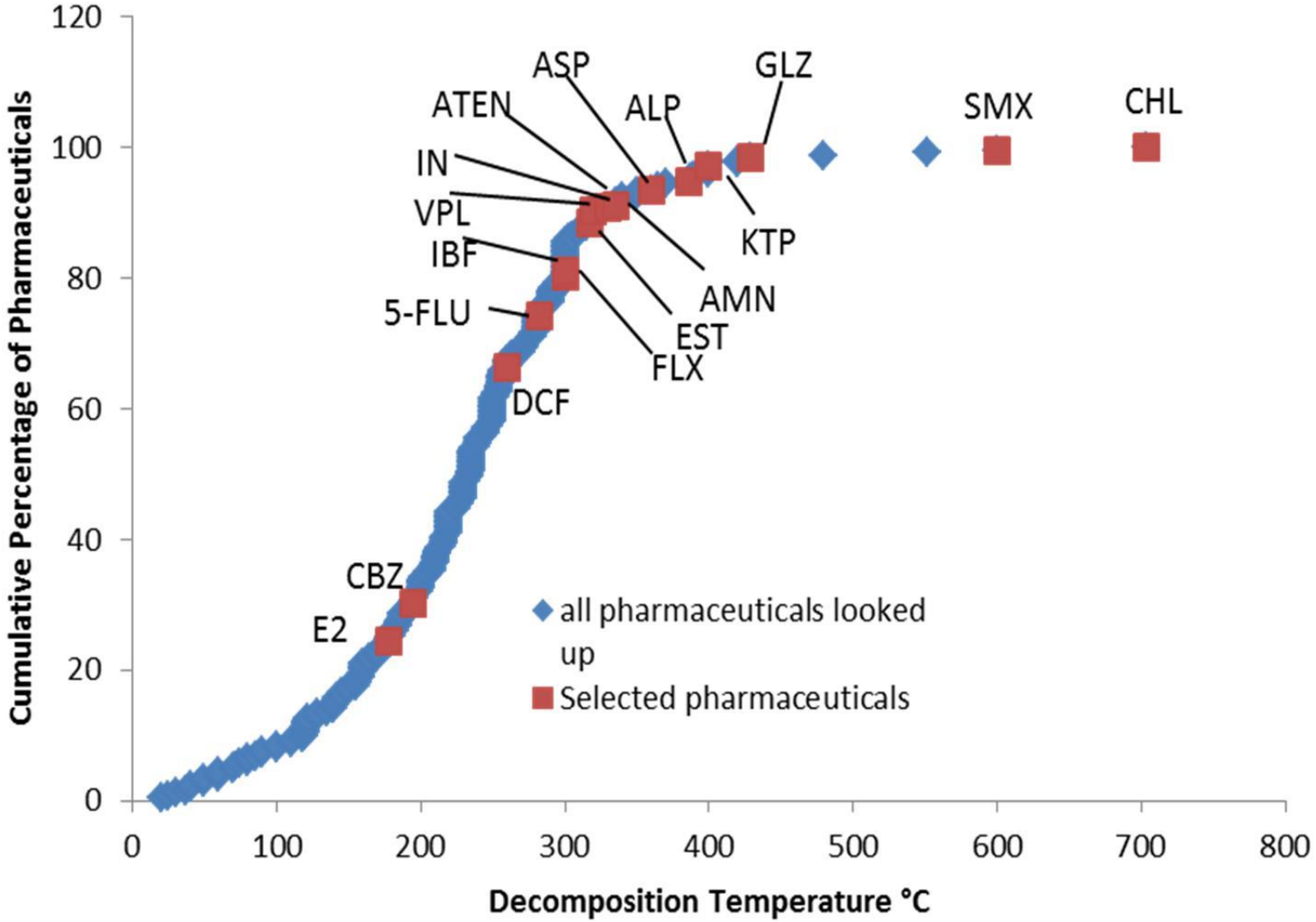
www.ourlocal pharmacy.com

PyroPure



PyroPure

Stability of study compounds



17 Pharmaceuticals selected

Decomposition Range 195-704°C

Non Steroidal Anti-Inflammatory Drugs

- Ketoprofen
- Ibuprofen
- Diclofenac
- Indomethacin

Analgesic

Ca-channel blocker: Verapamil

Beta-blocker: Atenolol

Anti-Parkinsons: Amantadine

Antidepressant: Fluoxetine

Anti-cancer: 5-fluorouracil

Antibiotics

- Chloramphenicol
- Sulfamethoxazole

Hormones

- Estradiol
- Ethinyl-estradiol

Anti-gout:
Allopurinol

Anti-diabetes:
Gliclazide

Anti-epilepsy: Carbamzepine

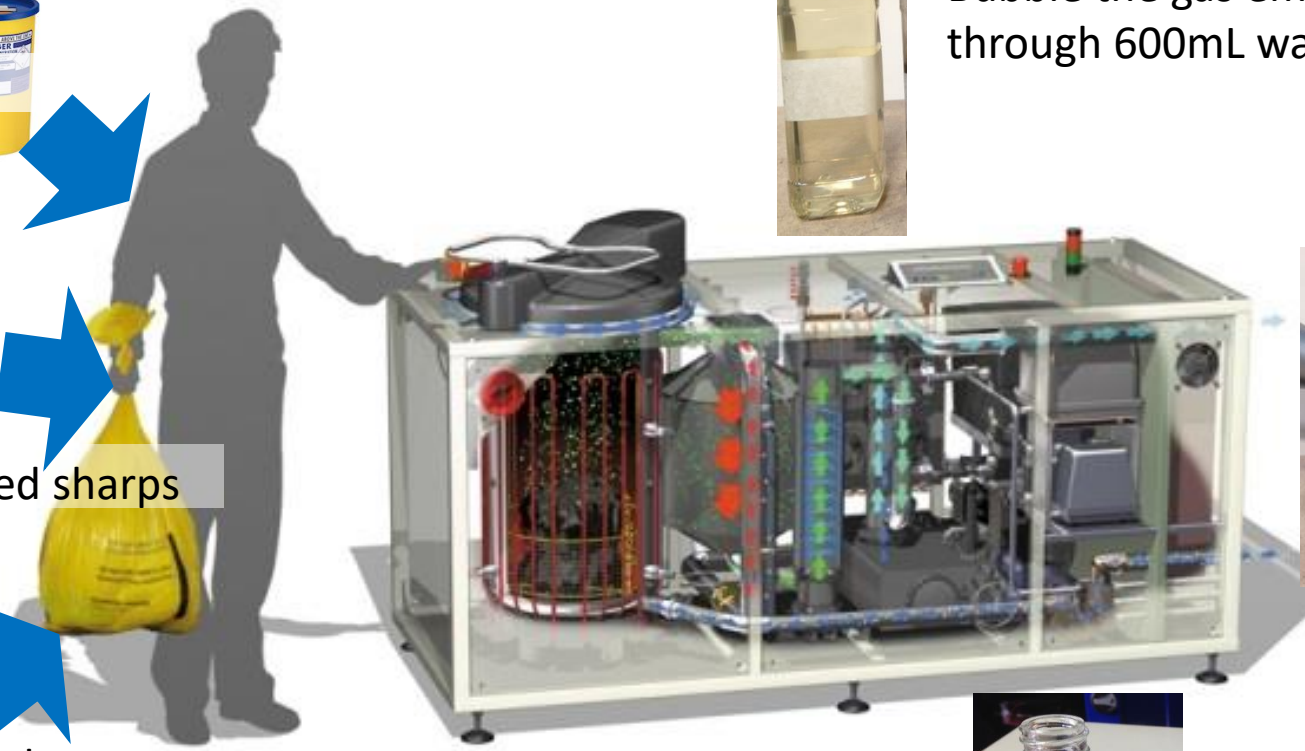
Experimental structure

3 Waste streams: For each 3 Pharmaceutical runs and 2 control runs

Take back medicines

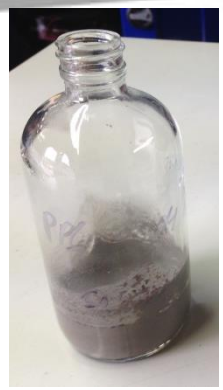
Contaminated sharps

Contaminated manufacturing waste



Bubble the gas emission through 600mL water

3 effluent samples per run



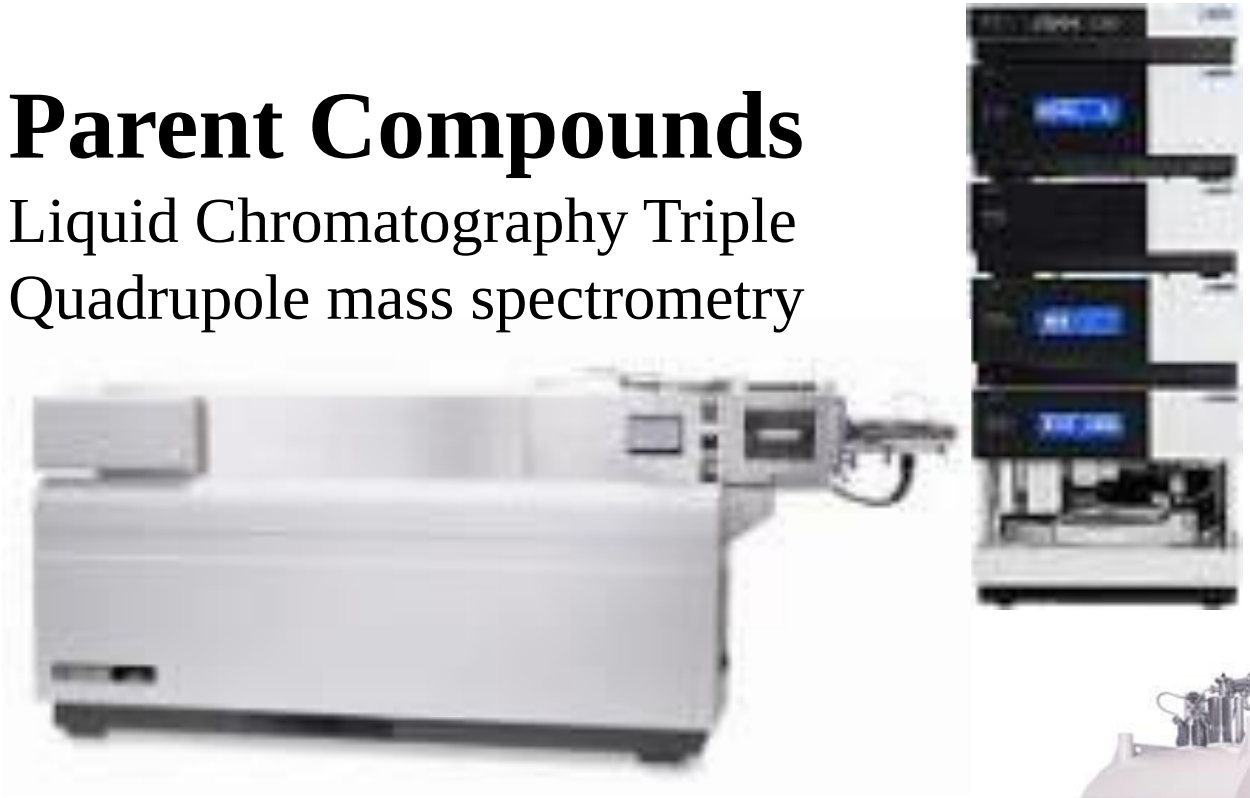
Collect all the solids (sludge)

Total of 15 runs: 5 for each waste stream

Analytical methods

Parent Compounds

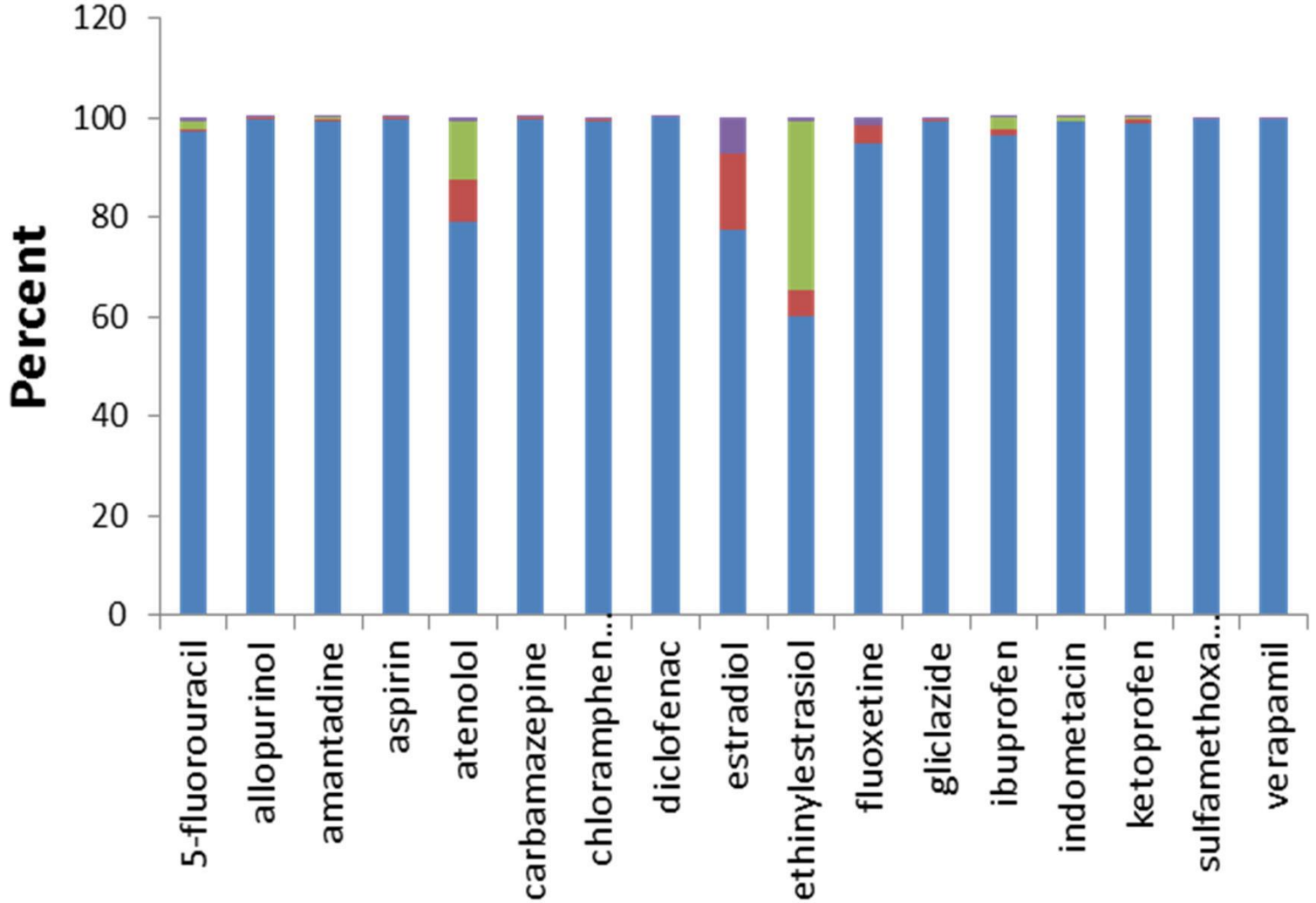
Liquid Chromatography Triple Quadrupole mass spectrometry



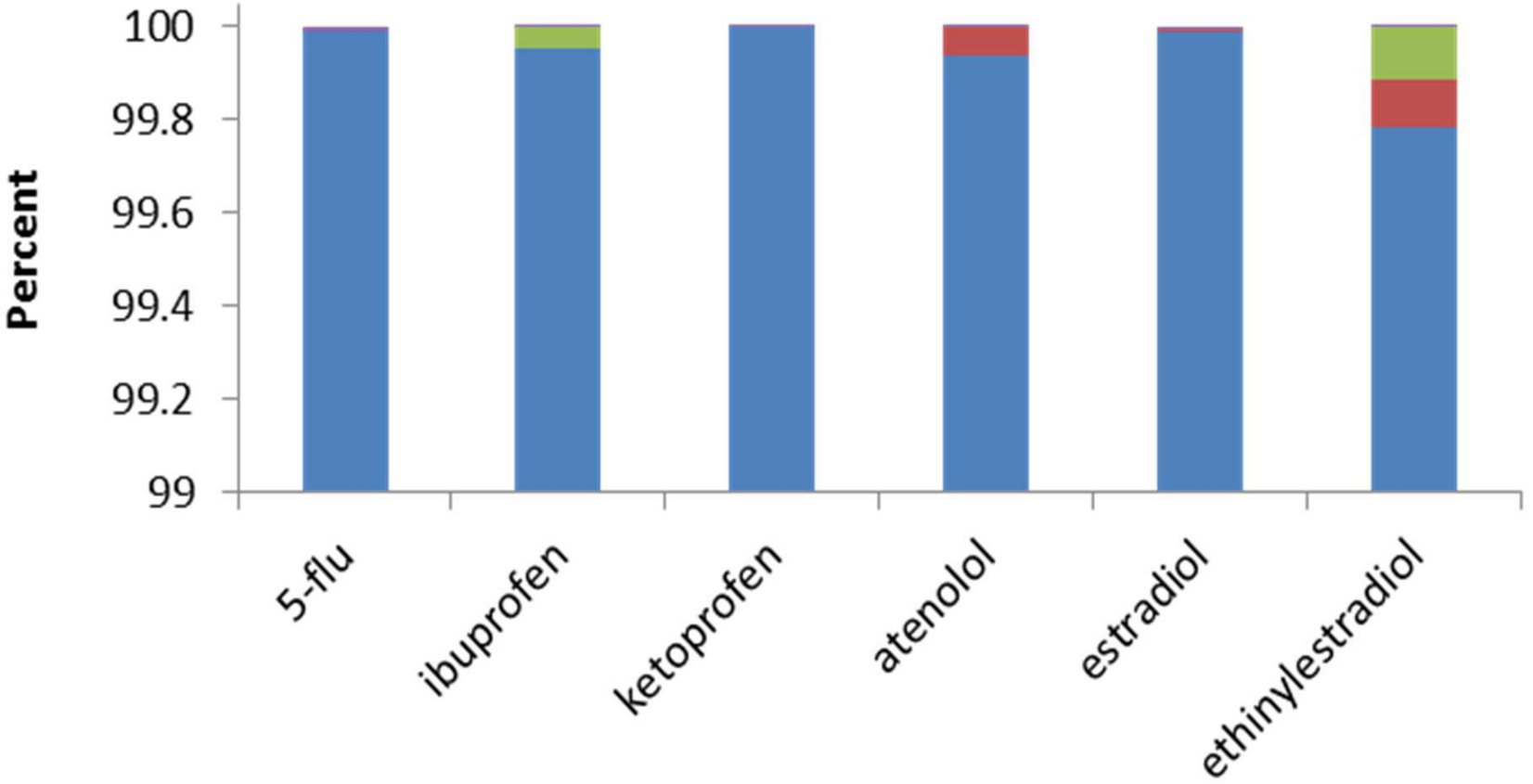
Transformation products

Fourier Transform Mass Spectrometry

Results - Phase 1



Results - Phase 2



Main results

- Greater than 99% destruction of all pharmaceuticals achieved in all waste simulations
- No known degradation products seen

Summary

- Major concerns over pharmaceuticals in the environment
- Using combination of modelling and monitoring we now have a good understanding of exposure of pharmaceuticals of concern
- A significant proportion of river reaches in the UK may be at risk so some compounds require further scrutiny
- Impacts on wildlife also possible
- A range of management options available - there is a need for an integrated approach
- Still many open questions

iPiE

- IMI project
- 10.3 M Euro project over 4 years
- Started 1 January 2015
- 25 partners from industry, academia, research institution and regulators

iPiE – The Aim

To develop frameworks that utilize information from toxicological studies, pharmacological mode of action and in silico models to support intelligence-based environmental testing of pharmaceuticals in development and to prioritise legacy pharmaceuticals for targeted environmental risk assessment and/or environmental (bio) monitoring.

Final product: iPiE software tool, database and guidance

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NERC SCIENCE OF THE ENVIRONMENT

fera The Food and Environment Research Agency

BBSRC bioscience for the future

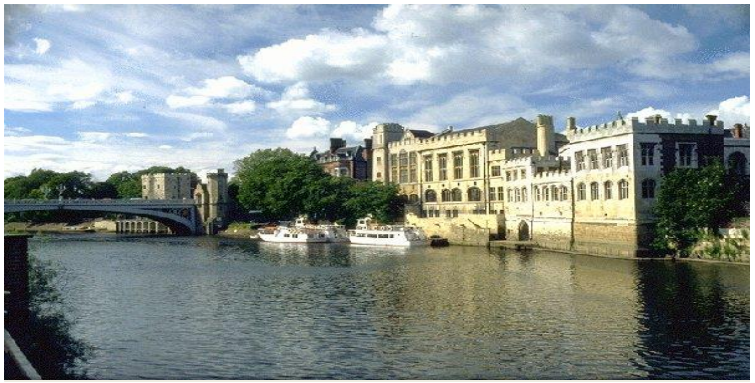
dwi

Technology Strategy Board
Driving Innovation

PyroPure

gsk GlaxoSmithKline


Environment



alistair.boxall@york.ac.uk